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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---------------------------|-------------|----------------------|---------------------|------------------|
| 10/087,466 | 03/01/2002 | Alexander Olek | 81659A | 6657 |
| 23685 | 7590 | 04/19/2007 | EXAMINER | |
| KRIEGSMAN & KRIEGSMAN | | | BRUSCA, JOHN S | |
| 30 TURNPIKE ROAD, SUITE 9 | | | ART UNIT | PAPER NUMBER |
| SOUTHBOROUGH, MA 01772 | | | 1631 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|----------------------------------------|------------|---------------|
| 3 MONTHS | 04/19/2007 | PAPER |

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| | | |
|------------------------------|------------------------|---------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 10/087,466 | OLEK ET AL. |
| | Examiner | Art Unit |
| | John S. Brusca | 1631 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 28 February 2007.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-12,14-18,20-23,25,26,30-34,36 and 41 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-12,14-18,20-23,25,26,30-34, 36 and 41 is/are rejected.

7) Claim(s) 1-12,14-18,20-23,25,26,30-34,36 and 41 is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a))

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ .

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .

5) Notice of Informal Patent Application (PTO-152)
6) Other: _____ .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 28 February 2007 has been entered.

Claim Objections

2. Claims 1-12, 14-18, 20-23, 25, 26, 30-34, 35, and 41 objected to because of the following informalities:

Claims 2-12, 14-18, 20-23, 25, 26, 30-34, 35, and 41 do not begin with an article which is required by rules of grammar, and further required to ascertain if a dependent claim requires all limitations of the claim from which it depends (when the article is "the") or if the dependent claim only requires a portion of the limitations of the claim from which it depends (when the article is "a").

Claims 1-12, 14-18, 20-23, 25, 26, 30-34, 35, and 41 recite biological samples that should be modified by an adjective in claim 1, but instead are modified by a noun "cancer" in the wherein clause. The term "cancer" should be amended to recite "cancerous."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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4. Claims 1-12, 14-18, 20-23, 25, 26, 30-34, 35, and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-12, 14-18, 20-23, 25, 26, 30-34, 35, and 41 are indefinite for recitation of the phrase "wherein said groups are either healthy and cancer or cancer" because the nature of the groups is not clearly defined. It is not clear if there are two or three groups, or if one group is healthy and cancerous. It is further unclear how a group can be both healthy and cancerous if there are only two groups listed. It is further unclear how at least two groups can be selected if the claim is limited to only two groups.

For the purpose of examination it has been assumed that the groups are healthy and cancerous.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-8, 10, 11, 14, 15, 17, 18, 20, 22, 23, 25, 26, 30-34, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kikyo et al. as evidenced by New England Biolabs and Siegfried et al. in view of Frommer et al. in view of Huang et al.

The claims are drawn to a method of determining differential gene expression between normal and cancerous tissue samples, analyzing methylation states of the gene, wherein the methylation state is determined by use of a bisulfite reaction, and adding identified differentially expressed and methylated genes to a database.

Kikyo et al. shows in the abstract and throughout a method of analysis of mouse embryo tissue for genes that are differentially expressed between normal embryos and abnormal embryos with chromosomal translocations. A differentially expressed neuronatin (Nnat) gene was shown to be imprinted by methylation analysis. Kikyo et al. shows on pages 68-69 differential display analysis of mRNA from the embryos, in which eighty primer pairs were used, and approximately 80-100 bands per primer pair were observed. Ten differentially expressed bands corresponding to differentially expressed genes were observed. Two genes were identified as H19 and Nnat (see figures 1A and 1B). Kikyo et al. further noted on page 69 prior art that used subtraction hybridization to identify Nnat as a differentially expressed gene, and verified Nnat differential expression by a reverse transcriptase-polymerase chain reaction method (see figure 1C). Kikyo et al. subsequently analyzed the Nnat gene for methylation by digestion with a panel of restriction endonucleases Hind III, BssH II, Eag I, and Sac II (see figure 6).

The New England Biolab website establishes that BssH II , Eag I and Sac II enzymes are inhibited by methylation at CpG sites.

Siegfried et al. establishes on page R305 that CpG methylation is a term of art meaning that a cytosine is methylated.

Kikyo et al. does not show use of a bisulfite reaction to determine methylation states of cytosine or analysis of tissues from normal and cancerous samples.

Frommer et al. states on page 1827 that cytosine methylation has long been recognized as an important factor in the silencing of genes in mammalian cells. Frommer et al. shows in the abstract and throughout a method to determine the positions of methylated cytosine residues in DNA by use of sodium bisulfite to convert cytosine to uracil in a chemical reaction (which does not react with methylated cytosine). Frommer et al. shows in page 1828 and figure 1 that their method comprises polymerase chain reactions subsequent to the sodium bisulfite treatment that produces polynucleotides suitable for sequencing reaction analysis. The sequence analysis of the amplified products reveals the presence of positions that originally contained methylated cytosine (see figures 2 and 3). Frommer et al. lists advantages of their method on page 1830, including the positive display of methylated cytosine residues, and the capacity to analyze individual strands of a DNA sample.

Huang et al. shows in the abstract that CpG methylation is known to be associated with gene silencing in cancer, and reviews the prior art showing the relationship between cancer and methylation states of DNA on page 459. Huang et al. shows analysis of methylation states in CpG regions in cancerous versus normal controls from cell lines in figures 3, 4, 5, and 7, and

primary breast tissue versus normal breast tissue in figures 6 and 8. Huang et al. shows a database of CpG clones that exhibit altered methylation in Table 1.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Kikyo et al. by use the sodium bisulfite reaction method of methylated cytosine detection of Frommer et al. because Frommer et al. shows that their method also detects methylated cytosine, and has further advantages of positive display of methylated cytosine residues and the ability to analyze individual strands of a DNA sample. It would have been further obvious to use samples of normal and cancerous tissue because Huang et al and Frommer et al. show that methylation regulates gene expression in mammalian cells and because Huang et al. shows that methylation is associated with gene silencing in cancer, and because Huang et al. shows analysis of CpG clones from normal and cancerous cell lines and primary clinical samples for differential methylation. It would have been further obvious to generate a database of the results of the method for the purpose of retaining the results for later review, as suggested by Huang et al. in table 1.

8. Claims 1, 6, 9, 16, 21, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kikyo et al. as evidenced by New England Biolabs and Siegfried et al. in view of Frommer et al. in view of Huang et al. as applied to claims 1-8, 10, 11, 14, 15, 17, 18, 20, 22, 23, 25, 26, 30-34, and 41 above and further in view of Danssaert et al.

The claims are drawn to the method of claim 1 with the further limitation that the methylation analysis comprises use of a robot or a computer device.

Kikyo et al. as evidenced by New England Biolabs and Siegfried et al. in view of Frommer et al. in view of Huang et al. as applied to claims 1-8, 10, 11, 14, 15, 17, 18, 20, 22, 23,

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25, 26, 30-34, and 41 above does not show a methylation analysis that comprises use of a robot or a computer device.

Danssaert et al. shows in column 1, lines 22-25 that polymerase chain reactions are best performed on automated devices that allow for consistent thermal cycling. Danssaert et al. shows computer controlled thermal cyclers that comprise robotic arms in column 1, line 33, column 4, and lines 39-50, column 5, lines 31-48.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Kikyo et al. as evidenced by New England Biolabs and Siegfried et al. in view of Frommer et al. in view of Huang et al. as applied to claims 1-8, 10, 11, 14, 15, 17, 18, 20, 22, 23, 25, 26, 30-34, and 41 above by use of a computer controlled thermal cycler, optionally with robotic arms, for conducting the polymerase chain reactions because Danssaert et al. shows that automated thermal cyclers have the advantage of providing consistent thermal cycling, and further because it is obvious to automate a manual activity (see MPEP 2144.04).

9. Claims 1 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kikyo et al. as evidenced by New England Biolabs and Siegfried et al. in view of Frommer et al. in view of Huang et al. as applied to claims 1-8, 10, 11, 14, 15, 17, 18, 20, 22, 23, 25, 26, 30-34, and 41 above, and further in view of Anderson et al.

The claims are drawn to the method of claim 1 with the further limitation that both mRNA and protein levels are measured.

Kikyo et al. as evidenced by New England Biolabs and Siegfried et al. in view of Frommer et al. in view of Huang et al. as applied to claims 1-8, 10, 11, 14, 15, 17, 18, 20, 22, 23, 25, 26, 30-34, and 41 above does not show measurement of protein levels.

Anderson et al. shows comparison of human liver gene expression by measurement of mRNA levels and corresponding protein levels (as measured by two-dimensional protein electrophoresis). Anderson et al. shows moderate levels of correlation between mRNA levels and protein levels in figures 1 and 2. Anderson et al. conclude on page 537 that determination of protein levels allows for a better understanding of multi-level gene expression control in complex organisms such as man.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Kikyo et al. as evidenced by New England Biolabs and Siegfried et al. in view of Frommer et al. in view of Huang et al. as applied to claims 1-8, 10, 11, 14, 15, 17, 18, 20, 22, 23, 25, 26, 30-34, and 41 above by additional use of the protein analysis method of Anderson et al. because Anderson et al. shows that determination of correlations between mRNA and protein levels allows for better understanding of gene expression controls.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

John S. Brusca 15 April 2007
John S. Brusca
Primary Examiner
Art Unit 1631

jsb